CAPSULES, HARD

Brian E. Jones
Shionogi Qualicaps, Alcobendas, Spain

INTRODUCTION

Hard or two-piece capsules have been produced since the 1840s (1). They were initially proposed for filling with oils and later were used for powders and other dry forms. The first patent was issued in France; however, the first industrial-scale manufacture took place in the United States in the 1870s. By the turn of the 20th century, millions of capsules per year were being filled in U.S. pharmacies because they met the need for an easily manufactured unit dosage form. Even though the use of capsules spread to other countries, they were considered an American specialty, and the manufacture of capsules did not spread to Europe and the rest of the world until the 1950s. The use of hard capsules increased greatly at this time because of the types of medicine such as antibiotics and antidepressants that were in vogue. This increase stimulated the production of fully automatic filling machines and self-locking capsules to meet the demands for high-speed industrial production. Hard capsules are welcomed by consumers because of their elegant appearance and shape, which is easy to swallow. The majority of capsule fills are dry powder blends, which are typically simple mixtures. The processing and filling of materials involve minimum stress and are the reasons why products are presented in this form. The formulator is able to prepare products that have the desired release characteristics, rapid, controlled, or modified, because of the limited number of factors involved. Hard capsules can be filled with formulations that have a wide range of physical properties from dry solids to nonaqueous solutions, thus enabling the formulator to use many different types of excipients to achieve the desired effect. Capsule products can be formulated to release their active ingredients at many sites along the gastrointestinal tract and to deliver them to the lungs.

RAW MATERIALS

Gelatin and Alternative Materials

Gelatin is a material derived from collagen, a natural protein, which is a fibrous material that occurs in the skin, bones, and connective tissues of animals (2). It is insoluble in water and is solubilized by hydrolysis. The raw materials used for its manufacture are obtained primarily from bovine bones or porcine skins. The reaction can be carried out at an acid pH level, yielding a type A gelatin (which is primarily produced from skins) and at a basic pH level giving a type B gelatin (which is primarily produced from bovine bones). Gelatin is a heterogeneous product that is a mixture of molecular species, α-, β-, and γ-peptides. The proportions and molecular weights are dependent on the nature of the chemical process. Gelatin was the first material used for the manufacture of capsules because of its unique properties. It is ideal because it is edible, soluble at body temperature, forms strong thin films, and undergoes a gelation process at temperatures just above ambient (1). It has a few technical drawbacks. It is of animal origin, and thus there are certain religious or dietary restrictions on its use. During the 1990s, there had been concerns over the use of bovine materials because of Bovine Spongiform Encephalopathy, which originated in the United Kingdom. The situation in Europe was brought under control by the European Commission (EC), which brought into effect rules that reduced risks to a minimum (3). The parts of the animal that theoretically could be the most infectious, such as the brain, are removed at slaughter and excluded from further processing. All the animals, from which bones are used in gelatin manufacture in Europe, are subjected to pre- and postmortem veterinary inspections. The alkaline hydrolysis process was made the method of choice for bones by the EC because of the pH levels and temperatures used in the process. There are a limited number of producers of pharmaceutical-grade gelatin worldwide thus enabling the problem to be addressed efficiently.

Hard capsules have traditionally been made from gelatin using a dipping process. Gelatin is very well-suited to this because it is an excellent film former and changes in state from liquid to solid at temperatures just above ambient (2). The film produced is homogenous and very robust, and gelatin capsules can readily withstand the mechanical stresses of the filling and packaging operations. The primary drawback in the use of gelatin is that it contains water, which acts as a plasticizer to the film. Thus, if they are not stored properly, their properties

will change. When water is lost from the shells, they become brittle, and thus they are not suitable for hydroscopic materials. Moisture-labile substances cannot be filled into them. For certain markets, there are consumer requirements for a capsule of vegetable origin. Since the last century, people have been searching for gelatin alternatives. The primary problem to be overcome has been the need to obtain a system that gels in a manner similar to that of gelatin so that the same manufacturing process and machines can be used. In the 1950s, capsules of methylcellulose were produced; however, their use was soon discontinued because of poor in vivo solubility (1). More recently, hard capsules have been produced from hydroxypropyl methylcellulose (HPMC), either by using a modified production process with heated mold pins (4a, 4b, 4c) or by the use of additives to make a true geling system (5a, 5b, 5c, 5d). Hard capsules made from HPMC have similar but different properties from gelatin capsules. Their primary advantage is that their moisture content is much lower, and even if this is removed, they retain their mechanical strength (6).

CAPSULE MANUFACTURE

Gelatin capsules are manufactured using a dipping process, which was first proposed by M. Lehuby in 1846 (1). The same process is in use today, but it has been improved and automated. It requires a large investment in machinery and a plant, which need to be operated on a continuous basis to make the process economic. This has resulted in capsules being made by only a limited number of companies worldwide.

The process starts by the preparation of a concentrated solution of gelatin in hot demineralized water. This solution is subjected to a low pressure to remove entrapped air bubbles. Small aliquots (20–30 L) of this solution are taken. To this colorants, either solutions of soluble dyes or suspensions of pigments, process aids such as sodium lauryl sulfate solution, and water to adjust the viscosity are added. The final solution has a concentration of 25–30 wt% of gelatin. This solution is then delivered to the capsule-manufacturing machine.

The manufacturing machines are housed in rooms supplied with filtered air, conditioned to 40–45% relative humidity (RH) and 22–25°C. The most commonly used machines are approximately 12 m long and 3 m high and are divided down the midline into two parts that are mirror images of each other (Fig. 1). The machines are divided lengthways into two levels, an top and a bottom. The caps are made on the left side and the bodies on the right side of the machine. The gelatin solutions are kept in temperature-controlled, jacketed hoppers (Fig. 1A). From there, they are fed to the capsule-forming container, variously known as a dip pan or dip pot (Fig. 1B). This is a stainless steel jacketed vessel that is oblong with a box in the center. The gelatin solution is pumped into the box and overflows the edge, thus maintaining a constant height. The stainless steel mold pins are mounted in a row of 30 on mild steel bars. Sets of bars are held in a device operated by a cam, which raises and lowers them. The mold pins, which are at 22°C, are lowered into the gelatin solution, which is at 50–55°C. The gelatin immediately gels on the mold. The molds are slowly raised, and, as they do, the excess gelatin runs off (Fig. 2). The quantity picked up by the mold is proportional to the viscosity. The higher the viscosity of the gelatin solution, the more gelatin is picked up. Thus, the viscosity of the solution is used to control the thickness of the gelatin film. As the mold breaks the surface, a blob of gelatin forms on the end of the mold. The sets of bars are transferred from the bottom to the top level of the machine and, as they do so, the bars are rotated to spread the film evenly over the end of the mold pin. The gelatin film is completely set by the time the molds reach the top level of the machine. Sets of bars are grouped together and mechanically transferred through a series of drying kilns (Fig. 1C). In these, air at controlled temperature and humidity is blown over them. When the bars reach the end of the machine, they are transferred to the bottom level and pushed back toward the front of the machine. When the bars emerge from the drying kilns, the moisture content of the gelatin films has been reduced from 70% at dipping to approximately 16 wt%. The molds, which had been warmed at the start of the drying process, have returned to ambient machine room temperature.

The dried gelatin films are removed from the mold pins and cut to the correct lengths, and the cap and body pieces are joined together. This is done in the automatic section of the machine (Fig. 1D). Pairs of bars, one with bodies and one with caps, are passed into the central section. Metal jaws pull the films off the mold pins into collets, which grip them. The collets rotate against a knife, and the gelatin film is cut. The excess is sucked away and recycled. The two pieces are transferred to a central joining block and are closed to a set length, called the unclosed joined length. The capsules are not fully closed because the filling machines would have difficulty separating them. They are closed so that the "prelock" indentations on the cap are engaged by the body, which provides sufficient holding strength so that they will not separate in handling.

The manufacture of HPMC capsules uses a similar process, and there are two different approaches. The viscosity of HPMC solutions increases with increasing

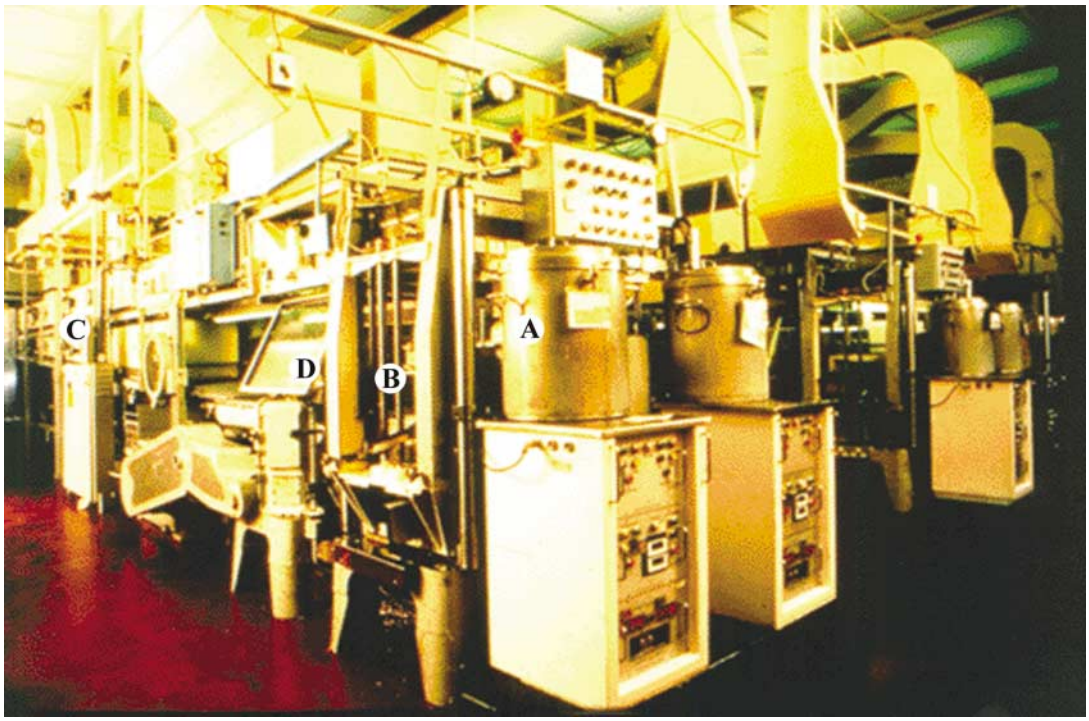

Fig. 1 A capsule manufacturing machine: A) Gelatin solution storage tank; B) dip pan; C) drying kilns; D) automatic section. (From Refs. 5a, 5b, 5c, 5d.)

temperatures. Thus, if hot mold pins at >60°C are lowered into HPMC solutions at 20–25°C material will gel on the molds. The manufacturing machines have to be modified to carry out this process (4a, 4b, 4c). The mold pins are also heated post dipping to hold the material in place before drying. Capsules made in this manner have a wall thickness twice that of standard gelatin capsules to give them sufficient mechanical strength for handling. In the other process using a geling system, an HPMC solution is prepared that contains carrageenan USNF as a gelation aid and potassium chloride as a gelation promoter (5a, 5b, 5c, 5d). Capsules are manufactured in the same manner and to the same dimensions as gelatin capsules. The only difference in the process is that the rate of output is slower because the rate of gelation is slower than that of gelatin.

STANDARDS FOR EMPTY CAPSULES

Two sets of standards are set for empty capsules: analytical and functional (6). Capsules, like all other pharmaceutical preparations, must comply with good manufacturing practice (GMP) norms and must be made of materials that comply with pharmacopeial chemical and microbiological standards. However, these tests do not indicate whether a capsule will run well on a filling machine. A series of functional tests are applied by the manufacturers. The critical dimensions of a capsule (the lengths and diameters of the caps and bodies) are checked. It is a continuous production process, and there will be a very small proportion of visually defective capsules. Standard statistical sampling methods are used to estimate quality from samples. The manufacturers and users agree on acceptable quality levels (AQL). The faults are divided into categories depending on the likely impact on capsule performance or the filling process. A different AQL is assigned to each category of fault.

STORAGE OF EMPTY CAPSULES

Empty gelatin capsules are designed to have a moisture content between 13 and 16%. The water acts as a plasticizer and is essential to maintain the flexibility and strength of the film. If falls below the limit, the capsules will become brittle; if its rises above the limit, they will soften. Empty HPMC capsules have a moisture content of 3–7%. These capsules can be dried to less than 1% moisture without losing their mechanical strength and

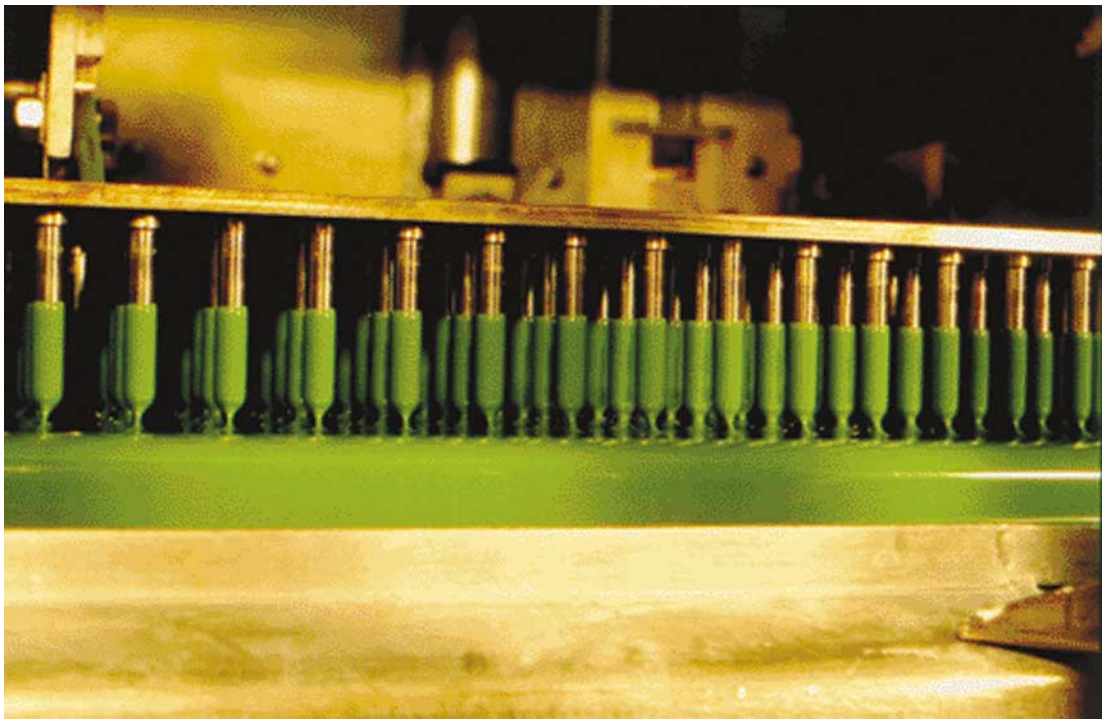

Fig. 2 Dip pan, capsule shell formation: (From Refs. 5a, 5b, 5c, 5d.)

becoming brittle (7). The water in hard capsules is tightly bound into the polymer structure and is insufficient for active bacterial growth (2).

The water content influences capsule dimensions as well. The dimensions vary slightly as moisture is lost or gained. As a general rule, the dimensions of gelatin capsules change by 0.5% for every 1% change in moisture in the range of 13.0–16.0% (1). HPMC capsules contain less water than do gelatin capsules, and the change in dimensions with moisture content is less. Thus, higher-speed filling machines must be operated in air-conditioned areas to achieve maximum performance. The moisture content of capsules depends on the conditions to which they are exposed (8, 9). Water will be lost or gained, and the absorption/desorption isotherm follows a marked hysteresis. In practice, this means that if capsules lose excessive amounts of water, they will not fully rehydrate when exposed to standard conditions, RH levels between 35 and 50%.

CAPSULE FILLING

The hard two-piece capsule can be filled with materials that have a wide range of physical properties. The types of formulations that have been filled into capsules are shown in Table 1. This is possible because of the manner in which filling machines handle empty capsules. First, capsules are orientated so that they are all pointing in the same direction, with the body downward. The capsules are transferred into pairs of bushes: the opening in the base of the top bush only allows the passage of the body, thus trapping the cap. The body is separated from the cap by means of suction. The open end of the body is then presented to a dosing mechanism and material transferred into it. The cap is then replaced on the body and the capsule closed to the correct closed joined length. This is an important dimension because it ensures that the self-locking mechanism, a series of indentations on the cap and body, is engaged correctly. This allows filled capsules to be transported and packaged on automatic equipment without separating.

Filling machines are differentiated by the means by which they measure the dose of material. They are available with a range of outputs, from bench scale to high-output industrial scale and from manual to fully automatic.

Powder Filling

The majority of formulations that are filled into capsules are dry powder mixtures. The methods of measuring the

Table 1 Formulation types for filling into hard capsules

Dry solids	Semisolids	Liquids
Powders	Thixotropic mixtures	Oily liquids
Granules	Thermosoftening mixtures	Nonaqueous solutions and suspensions
Pellets	Pastes	
Tablets		
Capsules		

dose can be divided into two groups: dependent and independent. The dependent machines use the capsule body directly to measure the dose of powder, whereas the independent machines use a separate device. The literature available on the mechanics of capsule-filling is limited compared with that available for tableting. Part of the reason for this is that tablets, unlike capsules, are used in a wide range of industries outside the healthcare sector, and thus there have been many more workers in the field.

The first industrial filling machines were of the dependent type. Powder is transferred from a hopper directly to the capsule body. The flow of the powder is aided either by a revolving auger or by a vibrating plate. The powder mass inside these capsules is a loose fill. The fill weights achievable on these machines is often higher than that obtained on automatic independent-type machines because the body is overfilled, and thus the total internal volume of the capsule shell is used (10). The first successful industrial filling machine was the ubiquitous machine designed by the doyen of pharmaceutical engineering, Arthur Colton, and the most popular version was the Model No. 8. This is a semiautomatic auger-filling machine (Fig. 3). The empty capsules are fed, aided by suction, into a pair of doughnut-shaped plates, which separate them. The plate containing the bodies is transferred manually to a turntable, and the powder hopper is pulled over the top of it. Powder is forced by the auger into the bodies as their plate revolves under the hopper. The fill weight is controlled by the speeds of rotation of the turntable and the auger. The only way to achieve good uniformity of fill weight on these machines is to completely fill the bodies. Partial filling is not an option. More recently, modifications have been made to the design to bring them in line with GMP requirements. The first was the Quali-fill^{TM} Model 8S developed by Eli Lilly & Co. in the 1980s. Since then, additional improvements have been made: the Quali-fill Model 10 from Schaefer Technologies, Inc. and the Ultra 8 II$^{®}$ from Capsugel. A fully automatic rotary auger-filling machine has been developed by Shionogi Qualicaps, the LIQFIL^{super} JCF40/80^{TM}. This machine has a three-roller system for capsule orientation and continuous feeding to a revolving disk assembly where the capsules are separated, filled, and rejoined. Other automatic dependent filling machines use vibration to aid powder flow into the bodies. The first such machine, the Osaka OCF 120, used a vibrating plate in the powder hopper. The bodies in their holders passed under the hopper. The cavities with the bodies were overfilled and raised up against a metal plate to push the excess inside powder inside. This system works well with dense, free-flowing material. Shionogi Qualicaps have made a modification to this method, the LIQFIL^{super} 40 and 80^{TM}, which uses spring-loaded fingers to compress the powder into the capsule body after it has been filled using a vibrating plate system.

Most automatic machines used in industry are of the independent type and compress a measured amount of powder to form a plug. The are two types of mechanisms: the dosing tube (or dosator) and the dosing disk and tamping finger.

The dosing tube is the most widely used, and it originated in Italy. Current manufacturers are IMA (Zanazi & Farmatic) (IMA North America, Inc.), MG2 (MG America, Inc.), Macophar (Romaco, Inc.), and Bonapace. The plug is formed inside a tube with a moveable piston that controls the dosing volume and applies a force to form the plug (Fig. 4). The lower-output machines have an intermittent motion, whereas the higher-output machines are rotary. The intermittent machines

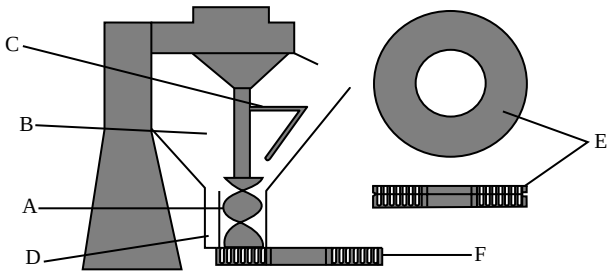

Fig. 3 Schematic diagram of auger filling system (Model No. 8): A) Auger; B) powder hopper; C) stirrer arm; D) pressure relief hole; E) capsule carrying rings; F) body ring holder.

tend to apply greater stresses to the powder than does the rotary machines because there is less time to form the plug, and thus formulations tend to require a higher level of lubricant. These machines are very versatile because the fill weight can be varied over a wide range by a simple adjustment to the position of the piston. The rotary machines can be linked to weighing devices and have automatic weight-control adjustment, which allows them to operate unattended.

The dosing disk and tamping finger machines form a plug in a similar but different manner. They are produced by a number of companies: Bosch (T.L. Systems Corp.), A.W. Bohanan Co., and Index Manufacturing Co., Inc. The dosing disk, which forms the base of the powder hopper, has up to six sets of machined holes (Fig. 5). In a holder, above the powder hopper, there are sets of stainless steel tamping fingers corresponding to the holes in the disk. These machines have an intermittent motion. After the machine has indexed, and the turret is stationary, the tamping fingers are lowered into the powder bed. The fingers are set to different levels, and they penetrate into the plate and consolidate the powder

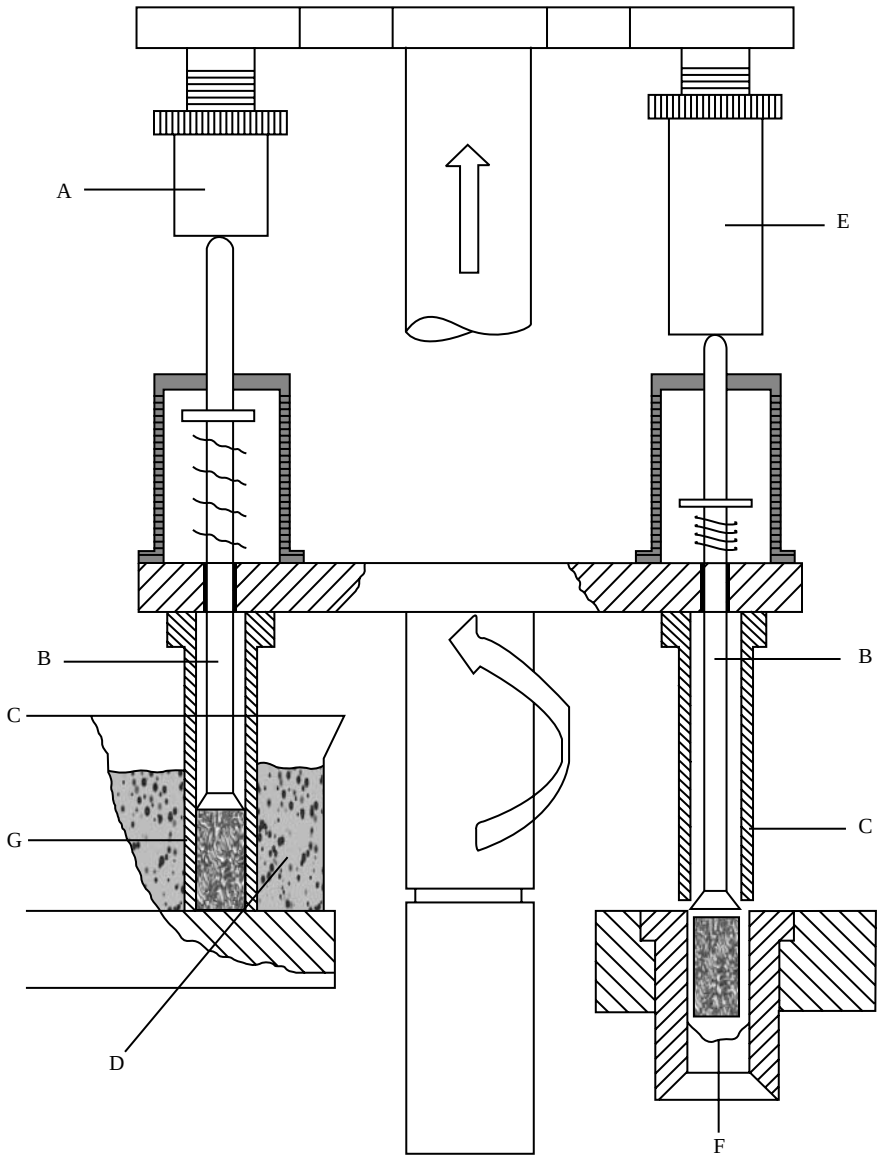

Fig. 4 Diagram of a dosator or dosing tube system (Zanasi RM63): A) Compression force platen; B) piston; C) dosing tube; D) powder hopper; E) plug ejection platen; F) capsule body in bush; G) powder plug.

in the cavities into plugs. Thus, the plug is formed in a series of tamps and not in a single motion as on the dosator machines. The dosing disks are produced in a range of thicknesses for each size of capsule. Thus, the selection of the correct thickness of disk is important because if the fill weight cannot be achieved, the machine has to be dismantled to change it. The selection of the optimum disk thickness for a formulation can be made either pragmatically using a simple test rig (11) or systematically by using an Instron tester to determine plug density and strength of a formulation at known compression forces (12).

Bench-scale filling machines

There are a variety of devices for the manual filling of small numbers of capsules. These typically consist of sets of plastic plates that have sets of holes drilled in them corresponding to the size of the capsule that can be filled. The capsules are fed into the plates, either manually one at a time or in groups using a feeding device. The bodies are clamped in the bottom plate and the top plate removed, which separates the caps from the body. The bodies are released so that they sit below the top of the bottom plate. Powder or pellets are filled into the capsules by spreading material over the body plate. Normally, a spatula is used to aid material flow. A larger version of this machine is available, the Model 301, made in stainless steel by Chemical and Pharmaceutical Industry Co., Inc. This has a tamping device, which enables higher fill weights to be achieved.

A small-scale automatic machine, the In-cap®, Dott. Bonapace (Schaefer Technologies, Inc.), is available. This machine measures the dose using a tamping finger and dosing disk device. The output is up to 3000 capsules per hour.

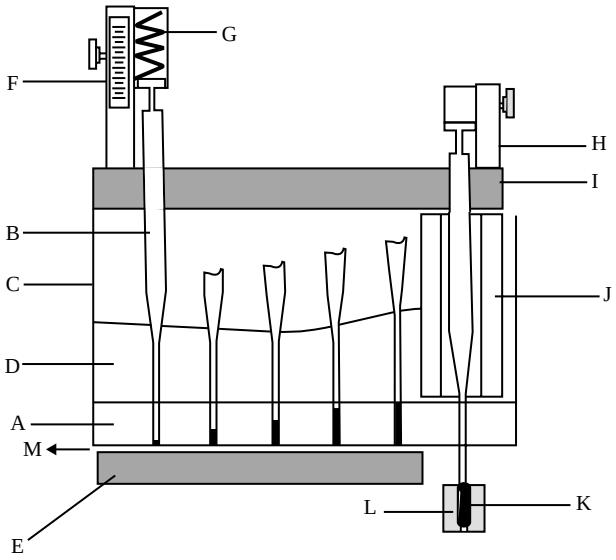

Fig. 5 Schematic diagram of a dosing disk and tamping finger system (Bosch GKF machine): A) dosing disk; B) tamping finger; C) powder hopper; D) powder bed; E) support plate; F) tamp depth adjuster; G) over load relief spring; H) ejection adjuster; I) guide block; J) transfer block; K) powder plug; L) capsule body in bush; M) suction.

Instrumented Filling Machines

Instrumented capsule-filling machines are not in widespread use, unlike tableting machines (13). This is partly owing to the facts that less basic work has been done, that there is an inherent problem in measuring the low forces, (1–100 N) used in forming and ejecting plugs, and that the powder bed is less controllable than that a tablet machine (10). Most of the published studies have been on intermittent motion dosing tube machines. Strain gauges have been applied to the piston and LVDTs to the moving parts of the system to measure the work involved in plug formation (13). Only one group has published work on an instrumented dosing disk and tamping finger machine (14). The problem with these machines is that the plug is formed at up to five different positions, and full instrumentation would be difficult. Capsule-filling machine simulators have been constructed to overcome some of the problems inherent is putting instrumentation on actual machines. Rotary operation machines present the biggest problem because of the movement of the dosing parts. One novel solution was to use the machine turret, with a single dosator, held stationary, and to construct a rig that moved the powder hopper around the dosator, simulating machine-running (15). A conventional stimulator for an intermittent motion dosator machine has been built that, in addition to the forces of axial compression and ejection, can measure the radial compression force (16). This has been used to study the consolidation and elastic properties of excipients. A tablet compaction simulator has been used to investigate plug formation at low forces and the results analyzed using standard tableting physics (17).

Dry Solid Filling

Granules, pellets, and tablets can be filled into capsules using automatic filling machines. Products are prepared in these forms to modify the release rates of active ingredients, to separate incompatible components, or to

densify a product to achieve the fill weight in a specific size of capsule.

The machines that can be used to fill these products can be divided into the direct and indirect categories. In the former, the material is fed into the body until it is completely full, e.g., Quali-fill Pellet Filler (Schaefer Technologies, Inc.) or any auger-filling machine with the auger removed. In the latter, the dose of material is measured in a chamber with a variable volume, which can be adjusted to give the required weight. Machines have modified dosators that either use suction to hold the material in the tube during transfer or are filled when they pushed up through the material bed. Other machines have special chambers with sliding plates to measure and release the material, e.g., Bosch GKF machines. After measurement, material is transferred to the capsule bodies either using gravity or assisted by air pressure, e.g., IMA Farmatic 2090 and MG2 G60.

The physical properties of these formulations are similar. Each type must be preferably nonfriable; tablets are usually film-coated. Two types of tablets are filled into capsules. Generally, the tablets are convex and have diameters that enable them to be introduced easily into the body and with sufficient clearance so that they do not tip onto their side (18). In the United States, after the Tylenol® incident in the 1980s, there is a need to fill large single tablets into a capsule so that there is no room for movement in the shell. The capsule shell is either banded or shrunk onto the tablet to prevent its removal. Granules and pellets should be regular in shape so that they flow and pack well. Their size should be related to the size of the capsule. Smaller-diameter pellets should be used for smaller capsules; otherwise, lower than expected fill weight will occur because of the "wall effect" of particle-packing (19).

Liquid Filling

All the major machine manufacturers have made machines that can fill capsules with liquids. There are two types of liquid fills: formulations of nonaqueous solutions and suspensions and formulations that are liquefied only for the filling process by either heat or shear stress (20). If the formulation is mobile at ambient temperatures, then the capsules will need to be sealed after filling.

The dose of material is measured using volumetric pumps, and thus the uniformity of fill is in most cases better than what can be achieved normally on a powder-filling machine. Typically, coefficients of variation of fill weight less than 1.0% are routinely achievable. This value will depend on the physical properties of the liquid, particularly its viscosity (22). Filling machines have been made that can handle materials with viscosities from 100 cp to 20,000 cp. Liquid-filling machines operate mostly at slower speeds than do the equivalent powder-filling machines. This is because the liquid has to pass through a much smaller orifice than that for a powder and thus takes longer. The rates are typically 50–66% of the rated output of the same size powder-filling machine.

Capsule fill capacity

The fill capacity of a hard capsule is dependent on the physical size of the capsule, the type of formulation, and the dosing mechanism on the filling device (Table 2) (10). The fill weight for powders has historically been calculated by multiplying a powder density value by the capsule volume as provided by the capsule manufacturers. This capsule volume is in fact the volume of the capsule body only, because the value was derived from work at the beginning of the 20th century when capsules were filled by hand in pharmacies. The relationship gives a reasonably accurate forecast machine filling if this volume number is multiplied by the tapped bulk density (TBD) of the powder. The reason for this is the dosing mechanisms on filling machines. The dependant machines, which can fill the total internal volume of the capsule, are able only to pack the powder at densities less than the TBD of the fill. The independent machines, which are able to apply a higher compressive force to the powder, form plugs whose dimensions must be less than the internal diameter and length of the capsule (Table 2). Thus, although the density of the plug will be higher than the TBD of the fill, the machines are unable to fill the total internal capsule volume.

The same rules of packing apply to pellet- and granule-filling. The size of the particles is important because of the increase in voidage caused by large particles in a small diameter tube. The smaller the capsule size, the smaller the corresponding size of the particles should be to achieve uniform fill weights.

There is a restriction in the fill capacity for liquids in capsules. To prevent the spillage of product, the maximum fill volume should not exceed 80% of the body volume.

Capsule Sealing

Many methods have been proposed for the hermetic sealing of capsules to prevent the leakage of liquids. The method proven to be the most successful is gelatin-banding (20). Two bands of gelatin solution are applied around the center of the filled capsule e.g., Hicapseal™ 40/100

Table 2 Capsule fill volume data

Size	Body volume (ml)[a]	Internal volume[b] (ml)	Max. plug length[c] (mm)	Max. plug volume[d] (ml)
0E	0.78	0.87	21.9	0.68
0	0.68	0.78	19.7	0.61
1	0.50	0.56	17.7	0.44
2	0.37	0.44	16.1	0.34
3	0.30	0.32	14.3	0.26
4	0.21	0.25	13.2	0.19

[a]From Capsugel Multistate File and Shionogi Qualicaps Capsules Technical Information Manual.
[b]Calculated from optimum theoretical capsule shape, each part a cylinder with a hemispherical end.
[c]Calculated from size of nondeforming plug, which fits inside a capsule closed to length specification of Shionogi Qualicaps Inc.
[d]Based on hole dimensions of Bosch (H&K) machine dosing disk.
(Adapted from Ref. 10.)

(Schaefer Technologies, Inc.). This band is dried using air at ambient conditions to prevent moisture loss from the shells, which would make them brittle. The band can be colored, permitting a more complicated appearance for product branding. This band complies with the requirements of the FDA *Tamper-Evident Packaging Requirements for Over-the-Counter Human Drug Products* (21) for tamper-evident sealed capsules.

Multiple Contents

Automatic filling machines are available that can have more than one product dosing device. Therefore, combinations of materials can be filled into the same capsule, such a mixture of a powder and a semisolid formulation or a powder and a tablet. The same formulation rules apply as to single forms. Combinations of materials allow the formulator to achieve specific goals in terms of product stability and types of release.

FORMULATION

Powder Properties

Powder formulations for capsule-filling must have good flow properties, be nonadhesive, and be cohesive enough to form plugs at low compression forces. In addition, they must be stable and release the active ingredient in the desired manner. The filling properties can be assessed on the bench scale by using a variety of tests ranging from simple to complex (11). Successful correlations between powders and filling performance have been made in several reports by determining various powder property constants calculated from tapped bulk-density volumetry (23–25). For various microcrystalline celluloses, Lüdde–Kawakita's constant *a* and Hausner's ratio were shown to be good indicators of machine-filling performance, especially when judging interchangeability of materials from various sources (23). Investigations on the packing properties of binary mixtures of different-shaped particles have shown that Lüdde–Kawakita's constant *a* can be used as an indicator of the maximum volume reduction (24). For microcrystalline cellulose, an angular particle, lactose monohydrate, improved packing, whereas spherical or needle-shaped particles tended to decrease the packing properties. The same methodology was used to investigate the bulk-volume changes of powders after granulation or low compression (25). This showed that capsule fill weights could be increased by high-shear granulation or by the use of machine compression and that the outcome was related directly to the initial powder properties. The filling of capsules with powdered herbs presents additional challenges because of the range of tissue materials used. The flow properties of these materials are poor, and a range of powder property constants was determined to try to find a parameter that correlated with filling-machine performance (26). It was found that tamp-filling machines were able to handle a greater variety of herbs than were dosator machines. The flow of powders under active conditions can be measured using specially constructed rheometers, and these data can be related to other powder properties (27).

The flow of powders on filling machine is aided by machine design. Most machines have devices to assist flow in the form of moving mechanical parts, vibration, or

suction pads. Another hindrance to obtaining good fill-weight uniformity on machines is adhesion of material to moving parts, particularly to the dose-measuring devices. It has been shown that the nature of the surface texture of the dosator is an important factor (28). The surface of the dosing parts can be coated with different metal finishes, similar to those used for tablet punches and dies, to reduce adhesion (29). The type of coating is related to the physical nature of the powder formulation.

In Vitro Testing

Pharmacopeias require that hard capsules be tested in the same apparatus as tablets, even though they have very different physical properties. Filled capsules contain entrapped air, and most formulations will float on water. Devices are required to ensure that they sink, and these can influence the results obtained (30). Gelatin and HPMC are adhesive materials and tend to block wire meshes that form part of the standard equipment. The manner in which capsules disintegrate and dissolve is dependent on several factors such as temperature and nature of the test media (31). The literature makes reference to the hard capsule effect; however, the literature shows that the rate-controlling step is the nature of the contents and not of the shell (32).

When capsules are placed in an aqueous solution at body temperature (37°C), the walls absorb water and swell (31). The rate of penetration is proportional to the thickness of the wall. In gelatin capsules, water droplets can be observed on the inside surface of the shell after 30–40 s. The wall ruptures first at the shoulders of the cap and body, which are the thinnest parts of the shell. The rate of gelatin solubility is dependent on the temperature of the solution (33). There is a significant decrease as the temperature falls below 35°C, and below approximately 30°C, they are completely insoluble and merely swell and distort. HPMC capsules, on the other hand, have a slower but uniform solubility between 10 and 55°C (34). The results for both types of capsules are influenced by the nature of the test media, e.g., the ionic strength of the ions present and the pH level (6, 31).

The rotating paddle method is the most frequently prescribed apparatus for measuring the dissolution rate of products in hard capsules. The test is used for manufacturing-control purposes and for assessing product stability. When gelatin capsules are stored at high temperatures and humidities (45°C, 75% RH), their solubility in water decreases with time. This is owing to the formation of a "pellicle" that slows release (35). This effect is called cross-linking and can be caused either by interaction between gelatin and compounds containing reactive groups such as an aldehyde (36) or by reorientation of the gelatin molecules to a more collagen-like structure (2). In the early 1990s, the FDA became concerned with this and initiated a test program to measure whether this had an effect on product efficacy (37). They filled acetaminophen into capsules that had been stressed by treatment with formaldehyde at two levels and into unstressed shells. They measured the dissolution in water and in simulated gastric fluid (SGF), with and without pepsin. This produced three sets of results, those that passed in all media (unstressed shells), those that failed in water but passed in the SGF (low-stress formaldehyde), and those that failed in all media (high-stress formaldehyde). The capsules were tested in human volunteers. The pharmacokinetic parameters C_{max}, T_{max}, and lag times could be ranked in order and the Area Under the Curve (AUC) were identical. However, the products were not considered bioequivalent because the results from the capsules that failed all the dissolution tests were outside the 80–125% confidence limits compared with the unstressed capsules. From this study, the *U.S. Pharmacopeia* introduced a two-tier test for hard-capsule dissolution (36). If the capsule product fails in water, then the test can be repeated using either a solution at pH 1.2, containing pepsin, or one at pH 7.2, containing pancreatin. An additional study using γ-scintigraphy showed that there was no difference in disintegration in vivo between untreated and medium-stressed capsules (38).

HPMC does not react with aldehydes or other agents that cause cross-linking of gelatin (6). HPMC capsules start to release their contents slightly slower than do gelatin capsules because of the slower rate of diffusion of water through the shell walls. However, once dissolution has begun, rates are similar, and the results are comparable. There are only minor changes in their dissolution after storage under accelerated conditions (6).

In Vivo Performance

Capsule products can be formulated to deliver active ingredients to various sites along the gastrointestinal tract or to the respiratory system (39). Buccal products can be made by filling standard capsules with semisolid matrix formulations, which give the product good sensory characteristics that allow them to be chewed or sucked and the contents retained in the mouth for absorption or action (40). The capsule shape is good for swallowing because one axis is longer than the other. This enables the tongue to line it up like a torpedo for entry into the throat. Many large tablets are capsule-shaped, the so-called

caplet, to take advantage of this. The literature shows that, provided the patient takes the capsules with water while up right, they do not stick in the throat any more than and, in fact, probably less than any other solid dosage form (41, 42). Capsules can be visualized inside the patient either using radio-opaque markers and x-rays or using radioisotopes such as technetium-99 and γ-scintigraphy. In the stomach, they disintegrate, and the contents spread depending on the patient's feeding state, fed or fasting (43). Capsule products can be retained in the stomach by the use of floating formulations. These are based on the use of hydrocolloids that swell on contact with water, forming a gel that releases the active drug by diffusion (44). Enteric products can be made either by coating the capsule shell with a polymer, which has the correct pH solubility characteristics, or by filling the capsule with coated particles (39). The challenge facing many formulators is the delivery of small peptides and proteins to the colon. This can be achieved by coating capsules with polymers that will only be broken down in the colon, e.g., mixtures of an azopolymer and a methacrylate polymer (45). Delivery to the colon can also be achieved by using a fill that includes an organic acid and a combination of pH-sensitive coatings, which together deliver the active drug to the proximal colon (46). Capsules can be administered rectally. They can be formulated to give immediate or prolonged release (47). The administration technique is different for other solid rectal forms, and they need to be coated with a glidant such as liquid paraffin.

Powders for inhalation products have been filled into capsules, which function as an inert biodegradable package. The active ingredient is in a micronized state, and it is filled either directly into the capsule or, more frequently, is attached to a carrier particle such as lactose (48). The formulations are filled using automatic machines and because the fill weight is small, i.e., less than 40 mg, microdosators are used. The product is taken using a special inhalation device. Powder is released from the shell either through holes, which are punctured into it by the device, or by the capsule parts being separated inside the device. The inhalers are breath-actuated. When the patient inhales, there is a turbulent airflow through the device that carries the active particles into the lung (49).

Formulation for Release

Most products are formulated to release their contents into the stomach. The rate-controlling step for release is the nature of the contents inside the capsule (32). In preparing a formulation, a formulator needs to take into account the physicochemical properties of the active ingredient, the nature and type of excipients required, and the filling process (10).

The properties of the active drug that are most significant are its aqueous solubility and particle size. The particle size needs to be chosen carefully. Smaller particles should dissolve faster because of their greater surface area but when filled inside a capsule they may aggregate, and the dissolving liquid may not be able to reach the individual particles (Fig. 6) (50). The available surface area of the active ingredient is more important than the actual surface area. Usually, the excipient that is the largest single quantity in the formulation is the filler (diluent), which functions both to increase the amount of fill material for potent actives and to aid in the formation of the powder plug. They can also play a role in the release of the active drug. People were first alerted to this in the late 1960s by the diphenylhydantoin incident in Australia, which showed that fillers need to be selected with solubility properties complementary to those of the active (51). Poorly soluble actives are best formulated with soluble excipients. The overall aim should be to make a powder mass that is as hydrophilic as possible. This can be done easily with potent actives because there is space available inside the capsule to accommodate excipients with the necessary properties, both in terms of flow and solubility. For higher-dose actives, excipients must be chosen that are active at low concentrations. Thus, disintegration and wetting agents need to be added. Excipients such as starch do not function as disintegrants in capsules as they do in tablets because the powder fill is much more porous. Sodium starch glycolate and croscarmellose, the so-called superdisintegrants, are used because of their greater swelling and wicking capability (52).

Certain excipients added to formulations to improve filling-machine performance can have an adverse effect on release because they are hydrophobic in nature. This is true of lubricants, which are added to formulations to prevent adhesion and to improve flow. The most used excipient in capsule formulations in both the United States and Europe is magnesium stearate (52, 53). This is hydrophobic, and there are many reports in the literature concerning its adverse effect on dissolution rates. However, the relationship between the concentration of magnesium stearate and release rate is not quite as simple as for tablets, in which an increase in amount brings a proportional decrease in release. The reason for this is the very different nature of tablets and capsules. A tablet is compressed using high forces to form a solid compact of relatively low porosity and must be if it is to survive subsequent handling. A hard capsule product, on the other hand, contains a powder mass of high porosity, which may

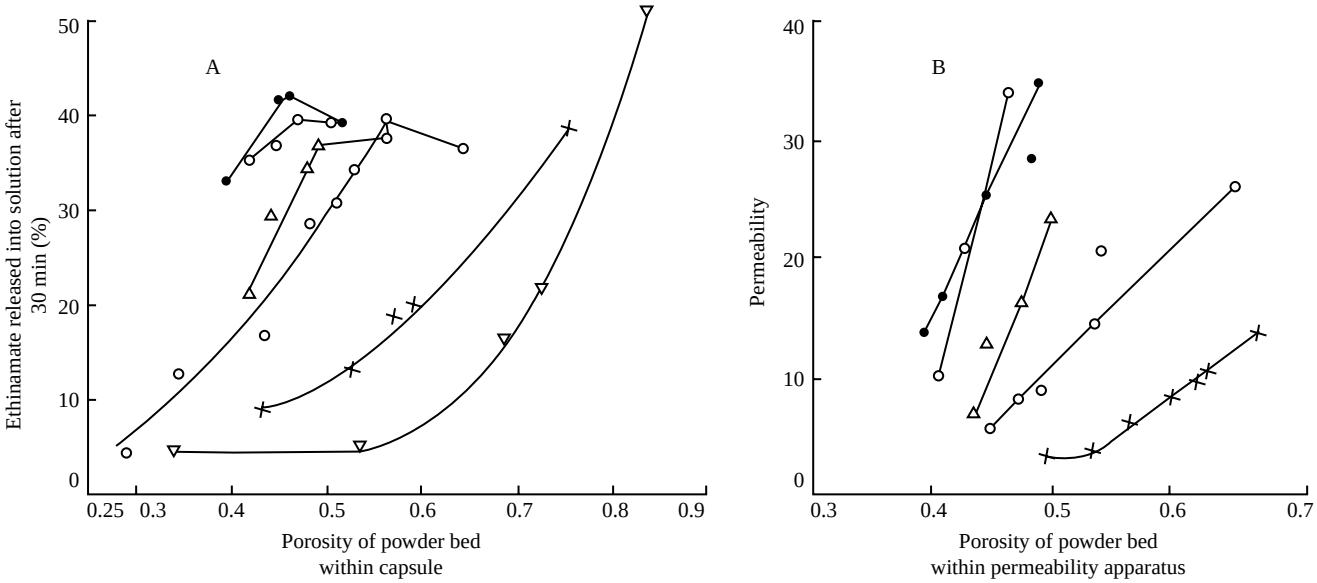

Fig. 6 The release of ethinamate from capsules containing different particle size fractions packed to give different porosities. A) The percentage of drug release after 30 min; B) The liquid permeability $m^2 \times 10^{11}$ of equivalent size fractions at known porosities. ●–● = 251–420 μm; □–□ = 177–251 μm; ○–○ = 152–177 μm; +–+ = 66–76 μm: ▽–▽ 8.3 μm;. (Adapted from Ref. 50.)

or may not have been compressed into a plug, and is contained within the shell that can withstand handling. Magnesium stearate functions as a lubricant when it is dispersed on the surfaces of other particles. At this site, it also reduces the cohesion of particles, and thus as its concentration increases, the powder mass will become weaker. Several workers have shown that an increase in magnesium stearate concentration has increased dissolution rates: small particles are made less cohesive (Fig. 7) (54), and powder plugs are weakened, thus breaking apart more readily when the capsule shell has dissolved (Fig. 8) (55). If the level in the formulation is not optimized, then there is a possibility that during the filling operation, the magnesium stearate will be gradually dispersed to a greater extent, resulting in changes in dissolution or weight uniformity (10, 56).

The method to improve the release rate of poorly soluble actives by dissolving or suspending them in polyethylene glycol was first suggested in 1970 (57). Since then, the filling of semisolid matrix formulations for filling into hard capsules has been developed, which enables this simple concept to be turned into a practical application (20). This formulation technique gives a different means to control the release of active drug from a capsule, either improving or delaying release. The technique involves dispersing or dissolving the active drug in excipients that are available in a range of melting points and Hydrophile-Lipophile Balance values (20). It is possible to modify the release rate of an active ingredient from such a matrix capsule by simply changing the properties of the single excipient (57).This technique has the added advantage that when working with potent and toxic material, it significantly reduces cross-contamination within an area (58). The actives once dispersed in a semisolid matrix are safe to handle without resorting to the use of expensive containment areas, i.e., any material that is spilt does not spread through the local environment, unlike a powdered material.

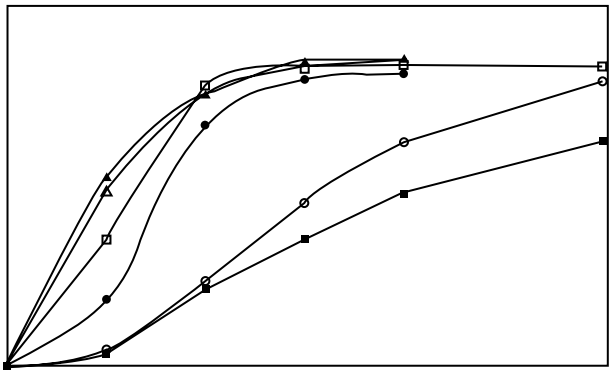

Fig. 7 Effect of particle size of rifampicin on its dissolution profile from capsules in the first fluid of JP IX by USP XVIII method. Rifampicin particle size: □-■, 42–80 mesh; △–▲, 80–100 mesh; ○–●, <200 mesh. Closed symbols with 0.5% magnesium stearate; open symbols without any addition. (Redrawn from Ref. 54.)

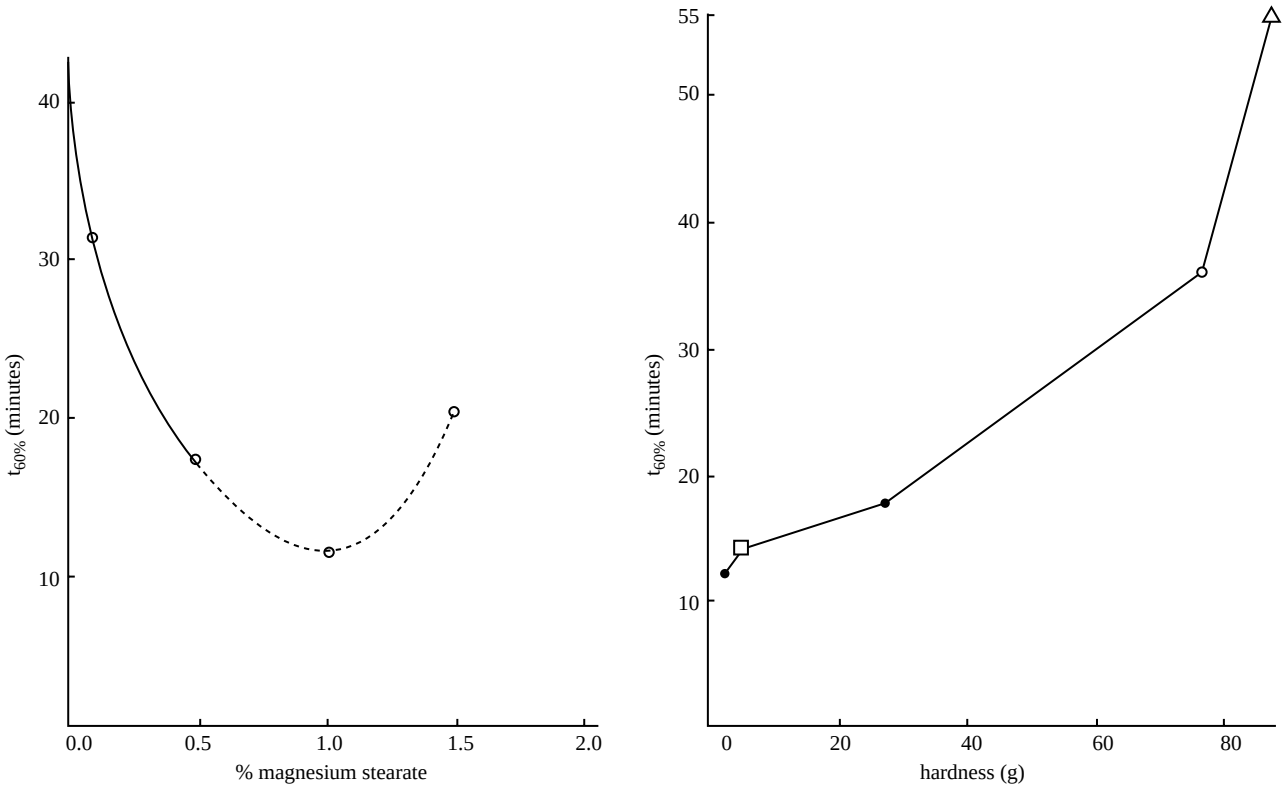

Fig. 8 Release of hydrochlorthiazide content from capsules, time for 60% to dissolve. All formulations filled on an instrumented Zanasi model LZ64 at the same compression force: A) effect of magnesium streate concentration, microcrystalline cellulose filler, compression force 15 Kg; B) effect of plug hardness, microcrystalline cellulose filler, compression force 21.7 Kg. (Adapted from Ref. 55.)

Formulation Optimization and Expert Systems

Product formulations must meet a number of goals. They must be able to be filled by machines to give a uniform, stable product. They must release the active ingredients in a manner to give the desired therapeutic effects. They must comply with the regulatory and compendial specifications. The excipients used in formulations often have properties that aid in compliance with one aspect but, at the same time, can have a negative effect on another goal. The relationship among the factors is complex. There are a variety of statistical tools that can be used to optimize formulations to achieve the best values of all the factors (59).

Another method of obtaining the best formulation is to use a so-called expert system to devise a formulation. The computer software is based on the use of neural networks and knowledge-based systems (60, 61). They serve two functions. First, they are able to reduce development time by suggesting the probable formulations, and second, they act as a teaching tool to pass on the knowledge of experts in the field.

REFERENCES

1. Jones, B.E. *Hard Capsules, Development and Technology*; Ridgway, K., Ed.; Chaps. 1, 4, and 6, Pharmaceutical Press: London, 1987.
2. Jones, R.T. *Hard Capsules, Development and Technology*; Ridgway, K., Ed.; Chaps. 2 and 3, Pharmaceutical Press: London, 1987.
3. *BSE Vademecum, Information for Consumers,* 3rd Ed.; Directorate General XXIV, European Commission: Brussels, 1998; 63.

4a. G.S. Technologies Inc., Method for the Manufacture of Pharmaceutical Cellulose Capsules US Patent 5,698,155 Dec. 16, 1997.
4b. Apparatus for the Manufacture of Pharmaceutical Cellulose Capsules US Patent 5,750,157 May 12, 1998.
4c. Method for the Manufacture of Pharmaceutical Cellulose Capsules US Patent 5,576.036 May 26, 1998.
5a. Shionogi Qualicaps Co., Ltd., Hard Capsule for Pharmaceutical Drugs and Method for Producing Same US Patent 5,264,223 Nov. 23, 1993.
5b. Hard Capsule for Pharmaceutical Drugs and Method for Producing Same US Patent 5,431,917 Jul. 11, 1995.
5c. Capsule Shell US Patent 5,756,123 May 26, 1998.
5d. Hard Capsules European Patent 0 592 130 B1.

6. American Federal Standard No. 285A. *Capsules (for Medicinal Purposes)*; General Services Administration: Washington, DC, 1976; 20.
7. Ogura, T.; Matsuura, S. HPMC Capsules—An Alternative to Gelatin. Pharm. Technol. Europe **1998**, *10* (11), 32, 34, 36, 40, 42.
8. York, P. Analysis of Moisture Sorption Hysteresis in Hard Gelatin Capsules, Maize Starch, and Maize Starch:Drug Mixtures. J. Pharm. Pharmacol. **1981**, *33*, 269–273.
9. Chang, R.-K.; Raghavan, K.S.; Hussain, M.A. A Study on Gelatin Capsule Brittleness: Moisture Transfer between the Capsule Shell and its Content. J. Pharm. Sci. **1998**, *87*, 556–55.
10. Jones, B.E. New Thoughts on Capsule Filling. S.T.P. Pharma Sci. **1998**, *8*, 277–283.
11. Jones, B.E. Powder Formulations for Capsule Filling. Mfg. Chem. **1988**, *59* (7), 28–30 & 33.
12. Davar, N.; Shah, R.; Pope, D.G.; Augsburger, L.L. The Selection of a Dosing Disk on a Hofliger—Karg Capsule-Filling Machine. Pharm. Tech. **1997**, *21* (2), 32, 34, 36, 38, 40, 42, 44 and 46.
13. Augsburger, L.L. Instrumented Capsule Filling Machines. Methadology and Application to Product Development. S.T.P. Pharma **1988**, *4*, 116–122.
14. Cropp, J.W.; Augsburger, L.L.; Marshall, K.M. Simultaneous Monitoring of Tamping Force and Pin Displacement (F-D) on an Hofliger and Karg Capsule Filling Machine. Int. J. Pharmaceut. **1991**, *71*, 127–136.
15. Jolliffe, I.G.; Newton, J.M.; Cooper, D. The Design and Use of an Instrumented mG2 Capsule Filling Machine Simulator. J. Pharm. Pharmac. **1982**, *34*, 230–235.
16. Britten, J.R.; Barnett, M.I.; Armstrong, N.A. Studies on Powder Plug Formation Using a Simulated Capsule Filling Machine. J. Pharm. Pharmacol. **1996**, *48*, 249–254.
17. Heda, P.K.; Muller, F.X.; Augsburger, L.L. Capsule Filling Machine Simulation. I. Low Force—Force Powder Compression Physics Relevant to Plug Formation. Pharm. Dev. Technol. **1999**, *4*, 209–219.
18. Hofer, U. Trockene Füllgüter. *Die Kapsel, Grundlagen, Technologie und Biopharmazie einer moderne Arzneiform*; Fahrig, W., Hofer, U., Eds.; Wissenschaftliche Verlagsgesellschaft mbH: Stuttgart, 1983; 83–111, Ch. V.
19. Cartensen, J.T. *Pharmaceutics of Solids and Solid Dosage Forms*; John Wiley & Sons: New York, 1977; 138–142.
20. Bowtle, W.J. Liquid Filling of Hard Gelatin Capsules—New Technology for Alternative Formulations. Pharm. Technol. Europe **1998**, *10* (10), 84, 86, 88–90.
21. 21 CFR Part 211, Docket No. 92N-0314, Federal Register, Vol. 63, Nov. 4 1998, 59463–59471.
22. Shah, N.H.; Phuapradit, W.; Ahmed, H. Liquid/Semi-Solid Filling in Hard Gelatin Capsules: Formulation and Processing Considerations. Bull. Tech. Gattefossé **1996**, *89*, 27–37.
23. Patel, R.; Podczeck, F. Investigation of the Effect of Type and Source of Microcrystalline Cellulose on Capsule Filling. Int. J. Pharm. **1996**, *128*, 123–127.
24. Podczeck, F.; Sharma, M. The Influence of Particle Size and Shape of Components of Binary Powder Mixtures on the Maximum Volume Reduction Due to Packing. Int. J. Pharm. **1996**, *137*, 41–47.
25. Podczeck, F.; Lee-Amies, G. The Bulk Volume Changes of Powders by Granulation and Compression with Respect to Capsule Filling. Int. J. Pharm. **1996**, *142*, 97–102.
26. Podczeck, F.; Claes, L.; Newton, J.M. Filling Powdered Herbs into Gelatine Capsules. Mfg Chem. **1999**, *60* (2), 29–31 & 33.
27. Podczeck, F. Rheological Studies of the Physical Properties of Powders Used in Capsule Filling. I, II. Pharm. Technol. Europe **1999**, *11* (9), 16, 18, 20–21 & 24 and 11(10), 34, 36, 38, 40 & 42.
28. Tan, S.B.; Newton, J.M. Influence of Capsule Dosator Wall Texture and Powder Properties on the Angle of Wall Friction and Powder-Wall Adhesion, and Capsule Filling Performance of Powders with Dosator Nozzles of Different Wall Texture. Int. J. Pharm. **1990**, *64*, 227–234 & 66:207–211.
29. Podczeck, F. Investigations into the Reduction of Powder Adhesion to Stainless Steel Surfaces by Surface Modification to Aid Capsule Filling. Int. J. Pharm. **1999**, *178*, 93–100.
30. Avgoustakis, K.; Anthanasiou, A.; Georgakopoulos, P.P. Effect of Helix Characteristics on the Dissolution Rate of Hard Gelatin Capsules. Int. J. Pharm. **1992**, *79*, 67–69.
31. Ludwig, A.; Van Ooteghem, M. Disintegration of Hard Gelatin Capsules. III. Penetration and Diffusion of Liquid through the Capsule Wall Investigated by Scanning Electron Microscopy. Pharm. Ind. Berl. **1980**, *42*, 1040–1043.

31a. Method of Measuring the Time of Rupture of the Capsule. Pharm. Ind. Berl. **1980**, *42*, 1140–1141.

32. Jones, B.E. Disintegration of Hard Gelatin Capsules. Chem. Pharm. Bull. **2000**, *48*, 951–956.
33. Jones, B.E.; Cole, W.V.J. The Influence of Test Conditions on the Disintegration Time of Gelatin Capsules. J. Pharm. Pharmacol. **1971**, *23*, 438–443.
34. Chiwele, I.; Jones, B.E.; Podczeck, F. S. S. M. Formulation and Capsules: An Improved Way to Handle Toxic Compounds.
35. Cartensen, J.T.; Rhodes, C.T. Pellicule Formation in Gelatin Capsules. Drug Dev. Ind. Pharm. **1993**, *19*, 2709–2712.
36. Digenis, G.A.; Gold, T.B.; Shah, V.P. Cross-Linking of Gelatin Capsules and its Relevance to their In Vitro–In Vivo Performance. J. Pharm. Sci. **1994**, *83*, 915–921.
37. Hard and Soft Gelatin Capsules: Issues, Research and Outcomes. Pharm. Res. **1997**, *14* (12), Podium Session, AAPS Convention, Boston, 1997.
38. Brown, J.; Madit, N.; Cole, E.T.; Wilding, I.R.; Cadé, D. The Effect of Cross-Linking on the In Vivo Disintegration of Hard Gelatin Capsules. Pharm. Res. **1998**, *15*, 1026–1030.
39. Jones, B.E. The Two-Piece Gelatin Capsule and the Gastro-Intestinal Tract. S.T.P. Pharma Pratiques **1991**, *1*, 128–134.
40. Wilson, C.G. Washington, N. Assessment of Disintegration and Dissolution Dosage Forms In Vivo Using Gamma Scintigraphy. Drug Dev. Ind. Pharm. **1988**, *14*, 211–281.
41. Evans, K.T.; Roberts, G.M. Where do all the Tablets Go? Lancet **1976**, *ii*, 1231–1239.
42. Hey, H.; Jørgensen, F.; Sørensen, K.; Hasselbach, H.; Wamberg, T. Oesophageal Transit of Six Commonly Used Tablets and Capsules. Br. Med. J. **1982**, *285*, 1717–1719.

43. Hunter, E.; Fell, J.T.; Calvert, R.T.; Sharma, H. "In Vivo" Disintegration of Hard Gelatin Capsules in Fasting and Non-Fasting Subjects. Int. J. Pharm. **1980**, *4*, 175–183.
44. Timmermans, J.; Möes, A.J. Factors Controlling the Buoyancy and Gastric Retention Capabilities of Floating Matrix Capsules: New Data for Reconsidering the Controversy. J. Pharm. Sci. **1994**, *83*, 18–24.
45. Kalala, W.; Kinget, R.; Van den Mooter, G.; Samyn, C. Colonic-Drug Targeting: In Vitro Release of Ibuprofen from Capsules Coated with Poly(Ether-Ester) Azopolymers. Int. J. Pharm. **1996**, *139*, 187–195.
46. Ishibashi, T.; Hatano, H.; Kobayashi, M.; Mizobe, M.; Yoshino, H. Design and Evaluation of a New Capsule-Type Dosage Form for Colon-Targeted Delivery of Drugs. Int. J. Pharm. **1998**, *168*, 31–40.
47. Leino, J.; Haavisto, H.; Tomminen, T.; Heinilä, K.; Eerikäinen, S.; Klinge, E.; Marvola, M. Development of Rectally Administered Prolonged Release Hard Gelatin Capsules Using Different Polymers as Diluents. S.T.P. Pharma Sci. **1997**, *7*, 348–353.
48. Srichana, T.; Martin, G.P.; Marriott, C. On the Relationship between Drug and Carrier Deposition from Dry Powder Inhalers In Vitro. Int. J. Pharm. **1998**, *167*, 13–23.
49. Srichana, T.; Martin, G.P.; Marriott, C. Dry Powder Inhalers: The Influence of Device Resistance and Powder Formulation on Drug and Lactose Deposition. Eur. J. Pharm. Sci. **1998**, *7*, 73–80.
50. Newton, J.M.; Rowley, G.M. On the Release of Drug From Hard Gelatin Capsules. J. Pharm. Pharmac. **1970**, *22* (Suppl.), 163S–168S.
51. Tyrer, J.M.; Eadie, M.J.; Sutherland, J.M.; Hopper, W.D. Outbreak of Anticonvulsant Intoxication in an Australian City. Br. Med. J. **1970**, *iv*, 271–273.
52. Shangraw, R.F.; Demarest, D.A. A Survey of Current Industrial Practices in the Formulation and Manufacture of Tablets and Capsules. Pharm. Technol. **1993**, *17* (1), 32–44.
53. Jones, B.E. Two-Piece Gelatin Capsules: Excipients for Powder Products, European Practice. Pharm. Technol. Europe **1995**, *7* (10), 25, 28–30 & 34.
54. Nakagawa, H.; Mohri, K.; Nakashima, K.; Sugimoto, I. Effects of Particle Size of Rifampicin and the Addition of Magnesium Stearate on Release of Rifampicin from Hard Gelatin Capsules. Yakugaku Zasshi **1980**, *100*, 1111–1117.
55. Mehta, A.M.; Augsburger, L.L. A Preliminary Study of the Effect of Slug Hardness on Drug Dissolution from Hard Gelatin Capsules Filled on an Automatic Capsule-Filling Machine. Int. J. Pharm. **1981**, *7*, 327–334.
56. Harding, V.D.; Higginson, S.J.; Wells, J.I. Predictive Stress Tests in the Scale-Up of Capsule Formulations. Drug Dev. Pharm. **1989**, *15*, 2315–2338.
57. Chiou, W.I.; Riegelman, S. Oral Absorption of Griseofulvin in Dogs: Increased Absorption Via Solid Dispersions in Polyethylene Glycol 6000. J. Pharm. Sci. **1970**, *59*, 937–942.
58. Duclos, R.; Bourret, E.; Brossard, C. Rheology of Polyol Behenates and Drug Release from Matrix Capsules. Int. J. Pharm. **1999**, *182*, 145–154.
59. Bowtle, W.J.; Burrows, S.L.; Holmes, E.D.; Jones, B.E. Pharm. Res. **1989**, *5* (12), PT612.
60. Hogan, J.; Shue, P-I.; Podczeck, F.; Newton, J.M. Investigations into the Relationship between Drug Properties, Filling, and the Release of Drugs from Hard Gelatin Capsules Using Multivariate Statistical Analysis. Pharm. Res. **1996**, *13*, 944–949.
61. Bateman, S.D.; Verlin, J.; Russo, M.; Guillot, M.; Laughlin, S.M. The Development and Validation of a Capsule Formulation Knowledge-Based System. Pharm. Technol. **1996**, *20* (3), 174, 176, 178, 180, 182 & 184.
62. Lai, S.; Podczeck, F.; Newton, J.M.; Daumesnil, R. An Expert System to Aid the Development of Capsule Formulations. Pharm. Technol. Europe **1996**, *8* (9), 60, 62, 64, 66 & 68.